

REMARKS

Status of the Claims

Claims 1, 2, 7-8, 10-33 and 56 were previously presented for examination and were rejected. Claims 3-4 and 34-55 were previously withdrawn as being drawn to non-elected inventions. Claim 7 has been canceled. Claims 1 and 8 have been amended to clarify the claims. Support for the amendments may be found in the specification as filed at page 5, lines 21-24, page 12, lines 12-14 and in original claims 7 and 8. Thus, no new matter has been introduced by way of these amendments. Upon entry of the amendments, claims 1, 2, 8, 10-33 and 56 will be pending. Entry of the amendments and reconsideration in view of the following comments is respectfully requested.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Rejections under 35 U.S.C. § 112, Second Paragraph

Applicants appreciate the Examiner's withdrawal of the previous rejections of claims 23 and 32 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

Applicants also appreciate the Examiner's withdrawal of the previous rejection of claims 1-2, 5-9, 11, 13-15, 22 and 24-33 under 35 U.S.C. § 102(b) as being anticipated by Antoine, et al.

Anticipation by Jenssen and Rios

Claims 1, 2, 7, 10, 11, 13-17, 22-28, 31-33 and 56 are rejected under 35 U.S.C. § 102(b) as being anticipated by Jenssen and Rios (*J. Immunol. Methods* 1989, 121:289-294; "Jenssen").

Janssen allegedly teaches “a method of preparation of leukocytes from patient fresh whole blood using paramagnetic, unmodified polystyrene microspheres having an average diameter of ____ nm, includes a washing step with PBS having a pH of about ____, includes a cellular recovery step, involves magnetic separation in the washing and recovery steps; the procedure takes approximately 10-20 min, is performed at room temperature, and does not include precipitation steps or poisonous agents” (the OA at ¶ 4). Thus, the Examiner has concluded that “Janssen and Rios teach each and every limitation of claims 1, 2, 7, 10, 11, 13-15, 22-28, 31-33 and 56.” (Id.)

Applicants respectfully traverse this rejection for the reasons set forth below.

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597 (Fed. Cir. 2002). To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. *In re Paulson*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (citing *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990)). “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131.

As an initial matter, claim 7 has been canceled and claim 1 has been amended to recite the following additional limitations:

a) contacting a sample containing or suspected of containing a target cell, cellular organelle or virus with a magnetic microbead, said magnetic microbead comprising a magnetizable substance selected from the group consisting of a ferromagnetic substance, a ferrimagnetic substance ~~and a metal composition~~ nickel, copper, tantalum, zirconium and an alloy thereof, and not comprising a biomolecule selected from the group consisting of an amino acid, a peptide, a protein, a nucleoside, a nucleotide, an oligonucleotide, a nucleic acid, a vitamin, a monosaccharide, an oligosaccharide, a carbohydrate, a lipid and a complex thereof, or any other moiety that binds to said target cell, cellular organelle or virus with high specificity...

Thus, claim 1 as amended no longer recites the genus of “a metal composition” and further makes it clear that the magnetic microbeads contemplated by the present invention do not comprise a biomolecule such as an amino acid, a peptide, a protein, a nucleoside, a nucleotide, an oligonucleotide, a nucleic acid, a vitamin, a monosaccharide, an oligosaccharide, a carbohydrate, a lipid or a complex thereof, in addition to any moiety that binds to the target cell, cellular organelle or virus with high specificity.

In the introduction, Jenssen teaches that “[t]he present report describes a measure of specificity of collection of cells using the polystyrene paramagnetic microspheres, in which cells from normal human bone marrow, or from one of two common tissue-cultured cell lines, are admixed with the polystyrene microbeads in the absence of antibody” (p. 291, left column). Further, Jenssen teaches that “[s]upper-paramagnetic microspheres were obtained from Dynal U.S.A.... [and] [t]he sterile beads were resuspended in affinity-purified sheep anti-mouse immunoglobulin antibody...” (p. 291, paragraph bridging left and right columns). Afterwards, “[s]heep anti-mouse IgG-treated Dynal microspheres were mixed with... cells” (p. 291, right column). Based on the foregoing, it becomes abundantly clear that the method taught by Jenssen comprises the use of: 1) paramagnetic beads; and 2) a biomolecule, namely an antibody to coat the paramagnetic beads.

The present specification at page 9, line 22 - page 10, line 5 explains:

As used herein, “paramagnetic substance” refers to the substances where the individual atoms, ions or molecules possess a permanent magnetic dipole moment. In the absence of an external magnetic field, the atomic dipoles point in random directions and there is no resultant magnetization of the substances as a whole in any direction. This random orientation is the result of thermal agitation within the substance. When an external magnetic field is applied, the atomic dipoles tend to orient themselves parallel to the field, since this is the state of lower energy than antiparallel position. This gives a net magnetization parallel to the field and a positive contribution to the susceptibility. Further details on “paramagnetic substance” or “paramagnetism” can be found in various literatures, *e.g.*, at Page 169 – page 171, Chapter 6, in “Electricity and Magnetism” by B.I Bleaney and B. Bleaney, Oxford, 1975.

The present specification at page 10, lines 6-20 further distinguishes ferromagnetic and ferrimagnetic substances from paramagnetic substances as follows:

As used herein, “ferromagnetic substance” refers to the substances that are distinguished by very large (positive) values of susceptibility, and are dependent on the applied magnetic field strength. In addition, ferromagnetic substances may possess a magnetic moment even in the absence of the applied magnetic field, and the retention of magnetization in zero field is known as “remanence”. Further details on “ferromagnetic substance” or “ferromagnetism” can be found in various literatures, *e.g.*, at Page 171 – page 174, Chapter 6, in “Electricity and Magnetism” by B.I Bleaney and B. Bleaney, Oxford, 1975.

As used herein, “ferrimagnetic substance” refers to the substances that show spontaneous magnetization, remanence, and other properties similar to ordinary ferromagnetic materials, but the spontaneous moment does not correspond to the value expected for full parallel alignment of the (magnetic) dipoles in the substance. Further details on “ferrimagnetic substance” or “ferrimagnetism” can be found in various literatures, *e.g.*, at Page 519- 524, Chapter 16, in “Electricity and Magnetism” by B.I Bleaney and B. Bleaney, Oxford, 1975.

Thus, it is clear from the above description that the magnetizable substances recited in claim 1 are distinct from the paramagnetic or super-paramagnetic microspheres taught in Jenssen. Accordingly, the IgG-coated, paramagnetic Dynal microspheres taught in Jenssen fail to anticipate the method of claim 1 because they do not teach each and every element of the claimed invention. Since Jenssen does not meet the strict identity standard of anticipation under 35 U.S.C. § 102, Applicants respectfully submit that this rejection 35 U.S.C. § 102(b) may be withdrawn.

Anticipation by Fletcher

Claims 1, 2, 7, 10, 11, 13-17, 22-26 and 56 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fletcher (*J. Gen. Microbiol.* 1976, 94:400-404). Fletcher allegedly teaches “a method of preparation of marine pseudomonads using paramagnetic (ferric oxide), unmodified polystyrene microspheres having an average diameter of ____ nm, includes a washing step with PBS having a pH of about ____, includes a cellular recovery step, involves magnetic separation in the washing and recovery steps; the procedure takes approximately 10-20 min, is performed at room temperature,

and does not include precipitation steps or poisonous agents” (the OA at ¶ 5). Thus, the Examiner has concluded that “Fletcher teaches each and every limitation of claims 1, 2, 7, 10, 11, 13-17, 22-26 and 56.” (Id.)

The legal standard for anticipation under 35 U.S.C. § 102(b) has been discussed in detail above, and that discussion is incorporated herein in its entirety.

As discussed above, claim 1 as amended recites magnetic microbeads not comprising a biomolecule such as an amino acid, a peptide, a protein, a nucleoside, a nucleotide, an oligonucleotide, a nucleic acid, a vitamin, a monosaccharide, an oligosaccharide, a carbohydrate, a lipid or a complex thereof, in addition to any moiety that binds to the target cell, cellular organelle or virus with high specificity.

Applicants respectfully submit that the Examiner has completely mischaracterized the teachings of Fletcher. Contrary to the Examiner’s allegations, Fletcher merely teaches that “bovine serum albumin, gelatin, fibrinogen and pepsin impaired the attachment of a marine pseudomonad to polystyrene Petri dishes” (abstract at p. 400). Fletcher does not disclose any microspheres, magnetic or otherwise; it only teaches bacterial interaction with flat polystyrene surfaces. In light of the foregoing, Applicants fail to see the relevance of Fletcher’s teachings to the present discussion. Since Fletcher does not teach each and every element of claim 1, the strict identity standard of anticipation under 35 U.S.C. § 102 is not met. Accordingly, Applicants respectfully submit that this rejection 35 U.S.C. § 102(b) may be withdrawn.

Rejections under 35 U.S.C. § 103

Obviousness over Janssen or Fletcher in View of Ullman

Claims 10, 12, 16, 17, and 22 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over either Janssen as applied to claims 1, 2, 7, 10, 11, 13-17, 22-28, 31-33 and 56, or Fletcher as applied to claims 1, 2, 7, 10, 11, 13-17, 22-26 and 56, above and in further view of Ullman, et al (U.S. Patent No. 5,536,644, issued Jul. 16, 1996, “Ullman”). The claims are allegedly

drawn to the method outlined above with the additional limitations: Microbead size between about 5×10^{-9} and 5×10^{-5} m, the microbead is modified to comprise a hydroxyl group, the sample selected from among various clinical specimen types specifically including blood, and the method completed within about 1 min. to about 20 min. The Examiner acknowledges that Janssen does not teach the aforementioned limitations. Ullman allegedly teaches use of a microbead sized between 2×10^{-8} and 1×10^{-4} m (a range that overlaps with the range of claim 10, see column 6, lines 65 ff), polymeric microbeads comprising hydroxyl groups (see column 7, lines 32 (alcohol) and 34 (free hydroxyl)), a clinical specimen (see, column 16, lines 62-64), a sample comprising blood (see column 13, lines 39-41), and the time of completing the method of 15-85 sec (this overlaps with the range of 1-10 min of claim 22; see column 18 lines 18-31 especially line 27).

The Examiner argues that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Janssen by using the limitations described above as taught by Ullman. The skilled artisan allegedly would have been motivated to do so because both methods have a common goal of isolating cells and it is inherently obvious to combine features of similar methods, and there allegedly would have been a reasonable expectation of success, given the success of the method taught by Ullman. Thus, the Examiner has concluded that the invention of claims 10, 12, 16, 17, and 22 was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully traverse this rejection for the reasons set forth below.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). A *prima facie* case of obviousness requires the satisfaction of three requirements. First, the combined prior art references must teach or suggest all of the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974); MPEP § 2143.03. Second, there must be some suggestion or motivation, either in the references or

in the knowledge generally available among those of ordinary skill in the art, to modify the reference. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731 (2007). And third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); MPEP § 2143.02.

I. The Cited References Do Not Teach or Suggest All of the Claim Limitations

“To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.” MPEP § 2143.03 citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As discussed above, Jenssen teaches that certain types of human cells can bind non-specifically to paramagnetic microbeads (Dynabeads manufactured by Dynal) coated with sheep anti-mouse immunoglobulin. It does not teach using the types of magnetizable microbeads recited in claim 1, not comprising a biomolecule or a moiety that binds to a target cell, cellular organelle or virus with high specificity. Fletcher merely teaches that cellular interaction with a flat polystyrene surface is adversely affected by certain types of biomolecules. The addition of Ullman fails to cure that fatal deficiencies of Jenssen and Fletcher. Furthermore, most of the specific teachings of Ullman cited by the Examiner relate to non-magnetic particles, not to magnetic microbeads as claimed in the present invention (*see* Ullman, column 6, line 63; column 7, line 25; column 13, lines 38-39, etc.). Accordingly, the combinations of Jenssen or Fletcher and Ullman do not teach all of the limitations of claims 10, 12, 16, 17, and 22, which means that the Examiner has failed to establish *prima facie* obviousness under 35 U.S.C. § 103(a).

II. There is No Motivation to Combine or Modify the Cited References to Achieve the Claimed Invention

To establish a *prima facie* case of obviousness, the Examiner must demonstrate some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731 (2007). “There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art.” MPEP § 2143.01 quoting *In re Rouffet*, 149 F.3d 1350, 1357,

47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). The Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103(a) “should be made explicit,” and that it was still “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *See KSR* at 1741.

In this case, it is not clear where the suggestion or motivation to combine would come from. Jenssen teaches that certain types of human cells can bind non-specifically to paramagnetic microbeads (Dynabeads manufactured by Dynal) coated with sheep anti-mouse immunoglobulin. Fletcher merely teaches that cellular interaction with a flat polystyrene surface is adversely affected by certain types of biomolecules. Ullman teaches a method of cell separation using Ferrofluid (colloidal iron oxide), namely magnetic particles coated with proteins such as succinylated bovine serum albumin or rabbit serum albumin (*see* Example 4). In contrast, the method claimed in the present invention teaches that non-specific separation of target cells, cellular organelles or viruses from a given sample can be accomplished using magnetic microbeads comprising magnetizable substances not disclosed in any of the cited references and not comprising any biomolecules whatsoever. Thus, a person of ordinary skill in the art would not have been motivated to modify the teachings of Jenssen or Fletcher using the teachings of Ullman to achieve the claimed invention. Accordingly, the Examiner has failed to establish *prima facie* obviousness.

III. A Skilled Artisan Would Not Have a Reasonable Expectation of Success in Achieving the Claimed Invention Based on the Combined Teachings of the Cited References

Obviousness does not require absolute predictability, however, at least some degree of predictability is required. MPEP § 2143.02 citing *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (Fed. Cir. 1976). Applicants respectfully submit that one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the claimed invention based on the teachings of Jenssen or Fletcher in view of Ullman.

As explained above, Jenssen teaches that certain types of human cells can bind non-specifically to paramagnetic microbeads (Dynabeads manufactured by Dynal) coated with sheep anti-mouse immunoglobulin. Fletcher merely teaches that cellular interaction with a flat

polystyrene surface is adversely affected by certain types of biomolecules. Ullman, et al. teaches a method of cell separation using Ferrofluid (colloidal iron oxide), namely magnetic particles coated with proteins such as succinylated bovine serum albumin or rabbit serum albumin (*see* Example 4). In contrast, the present invention claims a method of rapid cell separation wherein the magnetic beads are not coated with any biomolecules or moieties that bind to target cells, cellular organelles or viruses with high specificity (*see* amended claim 1). Thus, the combined teachings of Jenssen or Fletcher and Ullman do not provide the threshold level of predictability of success in achieving the claimed invention that is required in order to establish *prima facie* obviousness under 35 U.S.C. § 103(a).

Obviousness over Jenssen or Fletcher in View of Brinchmann

Claims 18-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over either Janssen as applied to claims 1, 2, 7, 10, 11, 13-17, 22-28, 31-33 and 56, or Fletcher as applied to claims 1, 2, 7, 10, 11, 13-17, 22-26 and 56, above and in further view of Brinchmann, et al. (*Journal of Virology*, 1991, 65(4): 2019-2023; “Brinchmann”). The Examiner asserts that Brinchmann teaches a method of separating HIV-infected cells from whole blood, washing the cell, isolating either HIV RNA or HIV DNA and amplifying the oligonucleotides (PCR of *pol* gene). The Examiner further invokes MPEP § 2144.04 quoting *In re Venner* for the proposition that “broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.” Accordingly, the Examiner argues that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Janssen or Fletcher by using the limitation of the claims as taught by Brinchmann. The skilled artisan allegedly would have been motivated to do so to detect specific nucleic acid sequences of the isolated cells as taught by Brinchmann, and there allegedly would have been a reasonable expectation of success, given the success of Brinchmann's group. Thus, the Examiner has concluded that the invention of claims 18-21 was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully traverse this rejection for the reasons set forth below.

The legal standard for obviousness under 35 U.S.C. § 103(a) has been discussed in detail above, and that discussion is incorporated herein in its entirety.

I. The Cited References Do Not Teach or Suggest All of the Claim Limitations

As discussed above, Jenssen teaches that certain types of human cells can bind non-specifically to paramagnetic microbeads (Dynabeads manufactured by Dynal) coated with sheep anti-mouse immunoglobulin. Similarly, Brinchmann, et al. teaches a method of isolating CD4⁺ T cells using Dynabeads coated with an anti-CD4 monoclonal antibody (*see* pages 2019-2020). Fletcher merely teaches that cellular interaction with a flat polystyrene surface is adversely affected by certain types of biomolecules. Thus, none of the cited references teaches a method of using magnetic microbeads not comprising a biomolecule or a moiety that binds to a target cell, cellular organelle or virus with high specificity. Accordingly, the combination of Jenssen or Fletcher and Brinchmann does not teach all of the limitations of claims 18-21, which means that the Examiner has failed to establish *prima facie* obviousness under 35 U.S.C. § 103(a).

II. There is No Motivation to Combine or Modify the Cited References to Achieve the Claimed Invention

Just as in the preceding discussion of Jenssen or Fletcher view of Ulmann, Applicants fail to see any teaching, suggestion or motivation to modify or combine the references. Once again, Jenssen teaches that certain types of human cells can bind non-specifically to paramagnetic microbeads (Dynabeads manufactured by Dynal) coated with sheep anti-mouse immunoglobulin. Similarly, Brinchmann, et al. teaches a method of specific cell isolation using a monoclonal anti-CD4 antibody. Fletcher merely teaches that cellular interaction with a flat polystyrene surface is adversely affected by certain types of biomolecules. In contrast, the method claimed in the present invention teaches that non-specific separation of target cells, cellular organelles or viruses from a given sample can be accomplished using magnetic microbeads comprising magnetizable substances not disclosed in any of the cited references and not comprising any biomolecules whatsoever. Thus, a person of ordinary skill in the art would not have been motivated to modify the teachings of

Jenssen or Fletcher using the teachings of Brinchmann to achieve the claimed invention. Accordingly, the Examiner has failed to establish *prima facie* obviousness.

III. A Skilled Artisan Would Not Have a Reasonable Expectation of Success in Achieving the Claimed Invention Based on the Combined Teachings of the Cited References

Applicants respectfully submit that one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the claimed invention based on the teachings of Jenssen or Fletcher in view of Brinchmann.

As explained above, Jenssen teaches that certain types of human cells can bind non-specifically to paramagnetic microbeads (Dynabeads manufactured by Dynal) coated with sheep anti-mouse immunoglobulin. Similarly, Brinchmann, et al. teaches a method of isolating CD4-positive T cells using a monoclonal anti-CD4 antibody. Fletcher merely teaches that cellular interaction with a flat polystyrene surface is adversely affected by certain types of biomolecules. In contrast, the present application claims a method of rapid cell separation wherein the magnetic beads are not coated with any biomolecules or moieties that bind to target cells, cellular organelles or viruses with high specificity (*see* amended claim 1). Thus, the combined teachings of Jenssen or Fletcher and Brinchmann do not provide the threshold level of predictability of success in achieving the claimed invention that is required in order to establish *prima facie* obviousness under 35 U.S.C. § 103(a).

The fact that Brinchmann teaches a method of separating HIV-infected cells from whole blood, washing the cell, isolating either HIV RNA or HIV DNA and amplifying the oligonucleotides using PCR automation is irrelevant to the present discussion because neither Brinchmann nor Jenssen nor Fletcher teaches protein-free magnetic separation claimed in the present invention. Furthermore, the discussion of *In re Venner* is not appropriate here because the method claimed in the present invention is distinguishable over the prior art regardless of whether it is practiced manually or automatically. Clearly, Applicants are not trying to claim an automatic or mechanical substitute to unpatentable manual activity which accomplishes the same result.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 514572000600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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